IN THE DRAWINGS

The attached sheet of drawings includes changes to Figs. 1, 2, 5-14. This sheet, which includes Fig. 1, 2, 5-14, replaces the original sheet including Figs. 1, 2, 5-14.

Attachment: Replacement Sheet

REMARKS/ARGUMENTS

Claims 1-4 and 10-14 are pending in this application. Support for the amendment to Claim 1 is found in original Claims 7 and 9 and the specification on page 8, lines 6-14. Claims 11-14 have been amended to remove multiple dependencies thereby obviating the objection under 37 CFR 1.75(c).

Amended drawings are provided Figures 1, 2, 5-14 to address the issues raised by the Examiner in the Office Action.

No new matter is believed to have been added by these amendments.

The rejections of Claims 1-6, and 8 under 35 U.S.C. 102(b) in view of Elias (U.S. Patent 2,656,299); and of Claims 1-6,7, 10 under 35 U.S.C. 102(a or e) in view of Callegaro, et al. (U.S. Patent 6,232,303) are no longer applicable in view of the incorporation of Claim 9 into Claim 1. While Elias and Callegaro appear to describe the combination of an antibiotic and a polysaccharide, there is no disclosure for the combination of an antibiotic and a hyaluronic acid and/or a hyaluronic acid gel, wherein the hyaluronic acid gel is crosslinked hyaluronic acid made of hyaluronic acid having a weight average primary molecular weight greater than 800,000.

Withdrawal of both grounds of rejection is requested.

The rejection of Claims 1-10 under 35 U.S.C. 103(a) in view of Nguyen (U.S. Patent 5,690,961) is respectfully traversed as well.

Nguyen appears to disclose the combination of an antibiotic and a cross-linked hyaluronic acid as a pharmaceutical composition. Nguyen does not disclose a molecular weight of 800,000 daltons or greater for the hyaluronic acid component of a gel. Nonetheless, the Office has taken the position that this limitation would have been obvious

based on the belief that hyaluronic acid exists in high molecular weight form *in vivo*. Applicants disagree and note that there is no suggestion or reason from the Nguyen disclosure for the claimed composition and as such there is no basis to conclude that the claims, as amended, would have been obvious.

In any case, Applicants are submitting with this response a Declaration under 37 CFR 1.132. This declaration assesses antibiotic retention of HA gels as described in Example 10 of the application of (1) Comparative Example 3 which as a average molecular weight of less than 800,000 and (2) Example 1, which is a HA gel having a weight average primary molecular weight of greater than 800,000. (see pages 1-2 of the Declaration). After assessment of the retention in the assay, Mr. Hashimoto states:

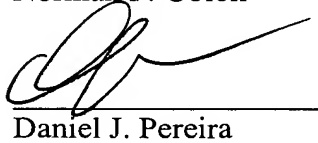
> These data show the improved antibiotic retention in gels containing weight average primary molecular weights greater than 800,000 compared to gels with lower molecular weights. As this improvement with higher molecular weight gels was not described by the publications cited by the U.S. Patent and Trademark Office, these results would not have been expected from what is described in those publications.

Withdrawal of this ground of rejection is requested.

Applicants also request a Notice of Allowance for all pending claims.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



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DOCKET NO: 259979US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HIROAKI MATSUNO, ET AL.	: EXAMINER: CHOI
SERIAL NO: 10/509,323	:
FILED: MAY 31, 2005	: GROUP ART UNIT: 1616
FOR: THERAPEUTIC COMPOSITION FOR BONE INFECTIOUS DISEASE	:

DECLARATION UNDER 37 C.F.R. 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, Masamichi Hashimoto hereby declare:
DENKI KAGAKU KOGYO

1. *I am employed by* KABUSHIKI KAISHA *as an* RESEARCHER and have experience in the field of BIOCHEMISTRY.

2. I am a named inventor of the above-identified application.

3. *I am familiar with the specification and prosecution of the above-identified patent* application.

4. The following observations and experiments were carried out by me or under my *direct supervision and control.*

5. The following supplemental experiments were carried out (Comparative Example 3 and Example 12). In Comparative Example 3, an hyaluronic acid (HA) gel having a weight average primary molecular weight less than 800,000 was prepared, and in Example 12, the molecular weight analysis and the antibiotic retention test on HA gels as described in Example 10 of the above-identified application were carried out.

6. Comparative Example 3

The GM-free HA gel obtained in Comparative Example 1 of the above-identified application was irradiated with gamma radiation at a dose of 5 kGy (60Co Gamma-irradiation Facility RICI, Radia Industry Co., Ltd.) to give a gamma irradiated HA gel. There was no change in the shape of the gel during the gamma irradiation.

7. Example 12

Antibiotic retention test in total arthroplasty models (HA gel sponge having a weight average primary molecular weight greater than 800,000)

The HA gel obtained in Example 1 and the gamma irradiated HA gel obtained in Comparative Example 3 were immersed in 15 ml of aqueous sodium hydroxide at a pH of 11 at 4°C for 1 hour to dissolve them. The resulting gel hydrolysate solutions were diluted with distilled water to 0.05 wt% and filtered through a membrane filter of 0.2 μm and 0.1 ml portions of them were used for molecular weight measurements by the GPC-MALLS method.

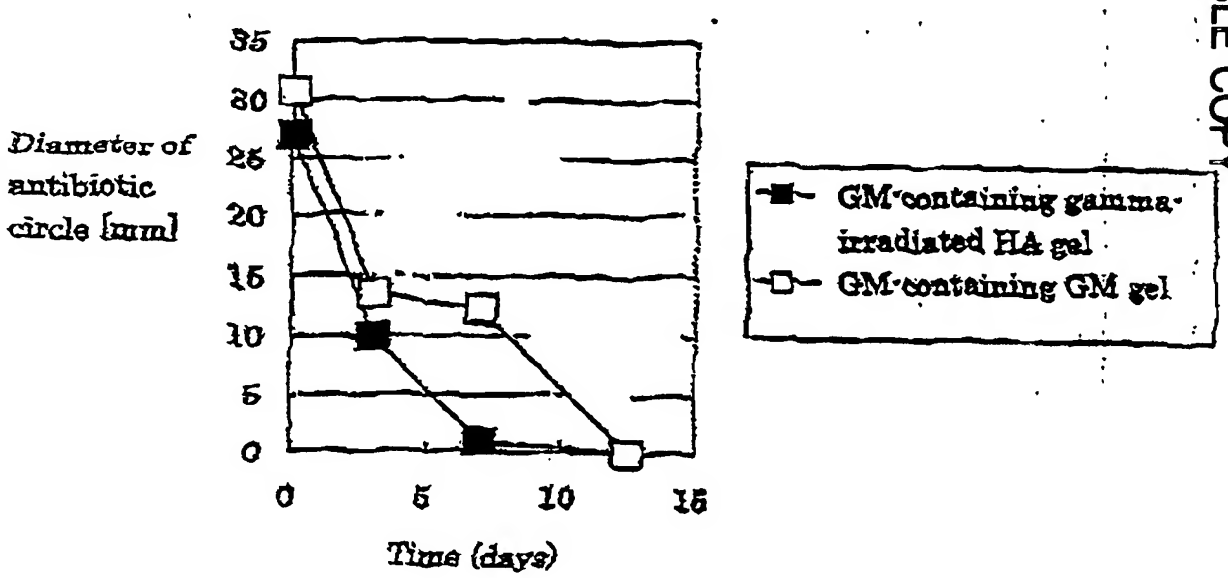
8. The HA gel obtained in Example 1 had a weight average primary molecular weight of 1,200,000, while the gamma-irradiated HA gel obtained in Comparative Example 3 had a weight average primary molecular weight of 400,000.

9. The HA gel obtained in Example 1 and the gamma irradiated HA gel obtained in Comparative Example 3 were punched with a biopsy trepan to make 4 mmxØ4 mm samples, and the samples were impregnated with aqueous solutions of 3 mg antibiotic (gentamicin (GM)) and freeze-dried. The retention of the antibiotic was assayed in the same animal test as described in Example 10 of the above-identified application.

10. The test results indicate that retention of the antibiotic in the bone marrow was better when the antibiotic infiltrated into the HA gel having a weight average primary molecular weight greater than 800,000 (Example 1) than when the antibiotic was infiltrated

into the HA gel having a weight average primary molecular weight of 800,000 or less (Comparative Example 3).

11. When the HA gel having a weight average primary molecular weight of 400,000 obtained in Comparative Example 3 was used, the antibiotic activity disappeared from the bone marrow within one week, while when the HA gel having a weight average primary molecular weight of 1,200,000 obtained in Example 1 was used, about 50% of the antibiotic activity remained after one week, as shown in Fig. 17 below:



12. These data show the improved antibiotic retention in gels containing weight average primary molecular weights greater than 800,000 compared to gels with lower molecular weights. As this improvement with higher molecular weight gels was not described by the publications cited by the U.S. Patent and Trademark Office, these results would not have been expected from what is described in those publications.

13. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under

Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Masamichi Hashimoto
Name

Masamichi Hashimoto
Signature

February 28, 2006
Date